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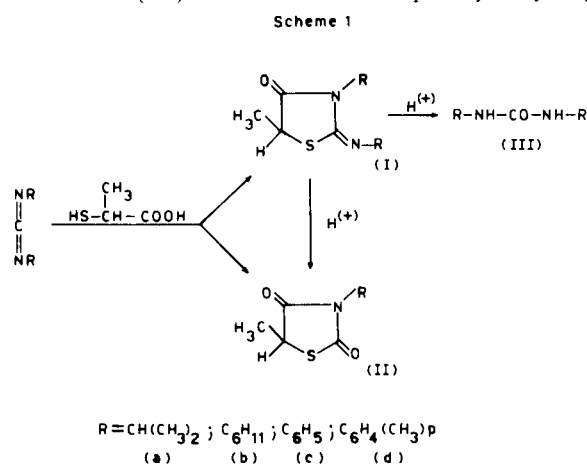
2,3-Substituted 5-methyl-4-thiazolidinones (I) and 3-substituted 5-methyl-2,4-thiazolidinediones (II) were prepared by reacting some carbodiimides with α -mercaptopropionic acid, with the purpose of obtaining potentially chemotherapeutic agents. It is noteworthy that 3-cyclohexyl-5-methyl-2,4-thiazolidinedione (II_d) was obtained in three different crystalline structures. Some secondary compounds were also obtained: the N,N' -disubstituted ureas (III) and thioureas (IV) in all cases, the dianilides (V) and the tri-substituted guanidines (VI) from the arylcarbodiimides, and the dithiolactide (VII) from the isopropyl- and cyclohexylcarbodiimides.

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The 3-substituted 2-imino-4-thiazolidinones (I) are the most interesting among all thiazolidinonic derivatives with respect to their therapeutic activity, especially as anti-tuberculous, antibacterial and antifungal agents (1). Some of these compounds have been prepared by a variety of synthetic procedures (2). They have usually been obtained (3), together with the related thiazolidinediones of biological interest (4a-e), by reacting mercaptoacetic acid with some carbodiimides. The enhancement of biological activity caused by the methyl group on C₅ (5) prompted us to synthesize some 2,3-substituted 5-methyl-4-thiazolidinones and 3-substituted 5-methyl-2,4-thiazolidinediones by using α -mercaptopropionic acid and N,N' -disubstituted carbodiimides.

Results and Discussion.

α -Mercaptopropionic acid reacted with one of the two carbodiimidic C=N groups to give 3-substituted 2-imino-5-methyl-4-thiazolidinones (I). The related 3-substituted 5-methyl-2,4-thiazolidinediones (II) were also formed except in the reaction with dicyclohexylcarbodiimide (Scheme 1). However, 3-cyclohexyl-5-methyl-2,4-thiazolidinedione (II_b) was also obtained upon hydrolysis (6)

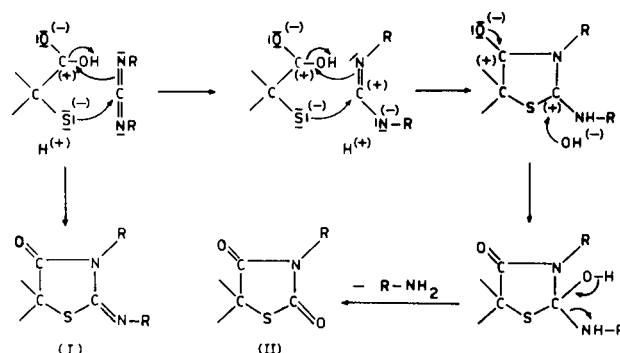


of thiazolidinone Ib with a mineral acid. Care must be taken in the I \rightarrow II hydrolysis step, so as not to involve

α -mercaptopropionic acid itself, the diones being otherwise the main products in the synthesis.

As discussed by Robba (7) concerning some dioxo-oxazolidines, the above mentioned diones II could also be formed by means of a bimolecular heterocyclization mechanism together with 4-thiazolidinones (8) (Scheme 2); amines have been detected as by products during the

Scheme 2



preparation of II. In our research, the dione II_b was not formed because of the increased stability of dicyclohexylcarbodiimide (9a,b) and the lower degree of polarization of the other carbon-nitrogen double bond.

All thiazolidine derivatives have been identified by chemical, physical and spectral means (Tables I, II, III). Furthermore, compounds Ic and IIc have been identified by comparison with samples obtained by an alternate synthetic procedure (10).

In contrast to the 4-thiazolidinones, the ir spectra of the 2,4-thiazolidinedione derivatives show a complex carbonyl pattern, due to the multiple carbonyl absorptions in the 1765-1675 cm^{-1} range (Figure 1). "Fermi resonance" effects are probably responsible for such complexity. This phenomenon is observed in other heterocyclic nuclei with two carbonyl functions (11a-c); e.g., similar thiazolidinediones (12) show two or more carbonyl absorptions not assignable to each carbonyl group. Furthermore, the 3-aryl-5-methyl-2,4-thiazolidinediones have a wide melting range even after repeated

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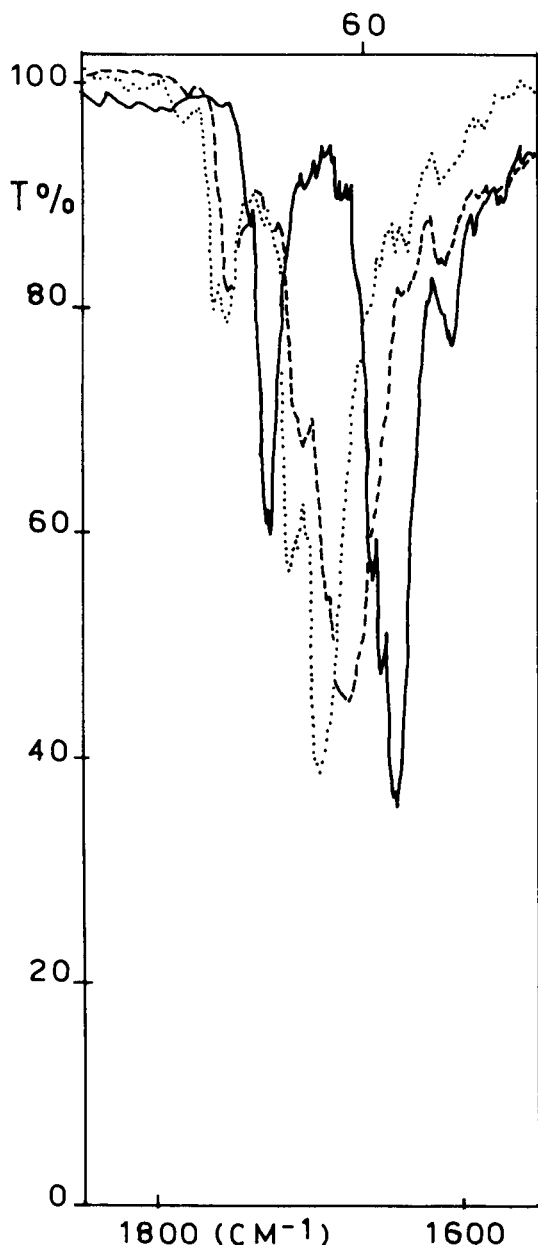


Figure 1. Ir spectra of: — (I); - - - (II) (F I); ··· (II) (F II) and (F III).

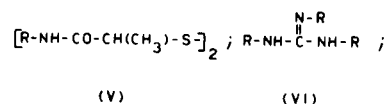
purification.

Painstaking separation procedures in working with the 3-*p*-tolyl derivative resulted in the isolation of three different crystalline structures: (a) a compound of m.p. 106-108° (F I) which formed agglomerate microcrystals and was obtained by heating the mixture to 140° at a rate of 4°/minute, followed by rapid cooling; (b) a compound of m.p. 118-120° (F II) which formed extended prismatic needles and was formed by rapid and complete elimination of the solvent; and (c) a compound of m.p. 145-

148° (F III) which formed rectangular prisms and was obtained by evaporating off a warm saturated solution in acetone of both F I or F II and leaving the residue to crystallize at 0°. The ir spectra (nujol mull) of F II and F III are identical, and differ from the spectrum of F I by variations of $\sim 20 \text{ cm}^{-1}$ in the C-H stretching and bending frequency, and variations of $\sim 20 \text{ cm}^{-1}$ in the carbonyl stretching frequency (Figure 1). Identical ir and pmr spectra in solution are obtained for all three forms.

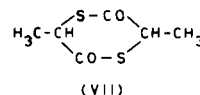
Apart from the above described thiazolidinic derivatives, other compounds were also isolated. The *N,N'*-disubstituted symmetrical ureas and thioureas were obtained from all syntheses. The ureas (III) result from carbodiimide hydration *via* different reaction pathways, which is in agreement with the literature (13a-b). The thioureas (IV) originate from the same carbodiimides by adding hydrogen sulphide, initially formed by desulphuration of α -mercaptopropionic acid.

Neither isopropyl- nor cyclohexylamine derivatives have been encountered, the former being a very volatile compound, while the latter cannot be formed in the absence of the 3-cyclohexyl-5-methyl-2,4-thiazolidinedione (IIb), as mentioned above. When the two arylamines were used in the synthetic procedure adopted, the following derivatives were obtained: (a) the dianilides (V) of dithiolactic acid formed by oxidation of α -mercaptopropionic acid anilides (14a-b); (b) *N,N',N''*-triphenyl- and tri-*p*-tolylguanidine (VI), previously described (15),



which arose from amines and carbodiimides; and (c) two unidentified reaction products having the compositions $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_2$ and $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_2$, respectively. The structural investigation of these compounds will be reported later, but they could probably originate from α -mercaptopropionic acid desulphuration.

In the syntheses realized by using isopropyl- and dicyclohexylcarbodiimide, a compound was isolated containing no nitrogen atoms. It was identified by spectral data (ir, pmr, ms) as the dithiolactide (VII) (1,4-dithiane-



2,5-dione-3,6-dimethyl) (16), and originated from α -mercaptopropionic acid *via* the loss of water induced by carbodiimide. The above compound, where two arylcarbodiimides were used, has not been isolated, because the presence of an amine causes ring cleavage and subsequent formation of the anilide (V), as was mentioned for the dithioglycolide (17).

Table I
Reaction Products from α -Mercaptopropionic Acid and Carbodiimides

	Isopropyl		Cyclohexyl		Phenyl		<i>p</i> -Tolyl	
	M.p., °C	B.p., °C	M.p., °C	B.p., °C	M.p., °C	Formula	M.p., °C	Formula
I	120		200		103 (a)	C ₁₆ H ₂₆ N ₂ O ₂ S	104 (c)	C ₁₈ H ₁₈ N ₂ O ₂ S
II	130		215		106 (a)	C ₁₀ H ₁₅ NO ₂ S	108 120 148	C ₁₁ H ₁₁ NO ₂ S
III	192 (a)				239 (a)	C ₁₃ H ₂₄ N ₂ O	266 (a)	C ₁₅ H ₁₆ N ₂ O
IV	142 (b)				155 (a)	C ₁₃ H ₂₄ N ₂ S	179 (a)	C ₁₅ H ₁₆ N ₂ S
V					160 (a)	C ₁₈ H ₂₀ N ₂ O ₂ S ₂	205 (c)	C ₂₀ H ₂₄ N ₂ O ₂ S ₂
VI					144 (a)	C ₁₉ H ₁₇ N ₃	123 (c)	C ₂₂ H ₂₃ N ₃
VII	42 (a)					C ₆ H ₈ O ₂ S ₂		
VIII					100 (c)	C ₁₈ H ₁₈ N ₂ O ₂	86 (c)	C ₂₀ H ₂₂ N ₂ O ₂

(a) Crystallized in ethanol. (b) Crystallized in water. (c) Crystallized in ligroin.

EXPERIMENTAL

The chromatographic separations were carried out on 20 x 20 2 mm plates of Merck silica gel (Kieselgel 60, F₂₅₄). Melting points were determined by using a Kofler hotplate and are uncorrected. Boiling points were determined using a Mettler FP 51 and are uncorrected.

IR spectra were recorded on a Perkin Elmer model 257 as nujol mulls or neat liquids. The pmr spectra were recorded on a Varian T-60 A spectrometer, using TMS as an internal standard; chemical shift values are expressed in ppm (δ), and coupling constants in Hz (cps). The structure of all described products was established by elemental analysis and by their spectroscopic data, as well as by comparison with authentic samples, when available (ir and pmr spectra, melting points, mixed melting points). Elemental analyses are given for all compounds not previously reported.

Reaction of α -Mercaptopropionic Acid with Carbodiimides.

α -Mercaptopropionic acid (0.1 mole) was added to 0.2 mole of the respective carbodiimides. An immediate exothermic reaction took place with formation of a dark liquid, a white solid and considerable evolution of hydrogen sulphide. Dry benzene (25 ml.) was added to dilute the thickening mixture. The suspension was left at room temperature for 1 hour and then heated on a steam bath for 2 hours resulting in further evolution of hydrogen sulphide. The solid was filtered and identified as a mixture of *N,N'*-disubstituted urea (III) and thiourea (IV), according to the carbodiimide used. The benzene solution was dried (sodium sulphate) and evaporated off to give a residue which, by thin layer chromatography with ethyl ether and petroleum ether (b.p. 40-70°) (1:1) as eluent, gave five spots for the isopropyl- and cyclohexyl-derivatives and seven spots for the other two. The mixture components were separated by repeated preparative tlc on Merck silica gel.

The five component mixture detected in the case of the isopropyl- and cyclohexyl-derivatives gave, in order of increasing R_f-values, the already known compounds III and IV, together with VII, II and I. Physical and chemical data are listed in Table I. Compound VII.

This compound was isolated as an oil which slowly crystallized, m.p. 38-42° (16); ir (nujol): 1680 cm⁻¹; pmr (deuteriochloroform): δ 1.50 (3H, d, CH₃) and 4.54 (1H, s, CH); ms: m/e (relative intensity) 176 (M⁺) (90), 148 (M⁺ - CO) (50), 120 (M⁺ - C₃H₄O) (25), 92 (M⁺ - C₃H₄O-CO) (100), 88 (M⁺/2) (70), 60 (COS, S=CHCH₃) (95), 45 (CHS) (50), 28 (CO) (50).

Compound Ia.

The spectral data for this compound are listed in Table II. *Anal.* Calcd. for C₁₀H₁₈N₂O₂S: C, 56.05; H, 8.47; N, 13.08; S, 14.93. Found: C, 56.00; H, 8.42; N, 13.12; S, 14.96.

Compound Ib.

The spectral data for this compound are listed in Table II. *Anal.* Calcd. for C₁₆H₂₆N₂O₂S: C, 65.28; H, 8.90; N, 9.52; S, 10.87. Found: C, 65.24; H, 8.93; N, 9.48; S, 10.91.

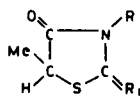
Compound IIa.

The spectral data for this compound are listed in Table III. *Anal.* Calcd. for C₇H₁₁NO₂S: C, 48.55; H, 6.40; N, 8.09; S, 18.47. Found: C, 48.52; H, 6.48; N, 8.04; S, 18.50.

Compound IIb.

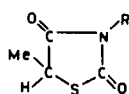
The spectral data for this compound are listed in Table III.

Table II
2,3-Substituted 5-Methyl-4-thiazolidinones



	R	R ₁	Ir (cm ⁻¹)		Pmr (δ) (Deuteriochloroform)		
			ν CO	ν CN	R	Assignments (No. of Protons) R ₁	CH-Me
Ia	CHMe ₂	N-CHMe ₂	1720	1645	(1) CH, 4.75 (m) (3) Me, 1.40 (d) J = 7 Hz	(1) CH, 3.40 (m) (3) Me, 1.16 (d) J = 6 Hz	(1) CH, 3.94 (q) (3) Me, 1.58 (d) J = 7 Hz
Ib	C ₆ H ₁₁	N-C ₆ H ₁₁	1720	1645	(22) C ₆ H ₁₁ + N-C ₆ H ₁₁ = 1-3.33 (m)		(1) CH, 3.96 (q) (3) Me, 1.59 (d) J = 7 Hz
Ic	C ₆ H ₅	N-C ₆ H ₅	1730	1635	(10) C ₆ H ₅ + N-C ₆ H ₅ = 6.66-7.66 (m)		(1) CH, 4.18 (q) (3) Me, 1.69 (d) J = 7 Hz
Id	<i>p</i> -C ₆ H ₄ Me	N- <i>p</i> -C ₆ H ₄ Me	1730	1645	(8) C ₆ H ₄ + N-C ₆ H ₄ = 6.66-7.58 (m) (3) Me, 2.41 (s)	(3) Me, 2.30 (s)	(1) CH, 4.09 (q) (3) Me, 1.70 (d) J = 7 Hz

Table III
3-Substituted 5-Methyl-2,4-thiazolidinediones



	R	Ir (cm ⁻¹)		Pmr (δ) (deuteriochloroform)	
		ν CO	R	Assignments (No. of Protons)	CH-Me
IIa	CHMe ₂	1740-1643		(1) CH, 4.50 (m) (3) Me, 1.40 (d) J = 7 Hz	(1) CH, 4.10 (q) (3) Me, 1.66 (d) J = 7 Hz
IIb	C ₆ H ₁₁	1750-1671		(11) 1-2.66 (m)	(1) CH, 4.15 (q) (3) Me, 1.68 (d) J = 7 Hz
IIc	C ₆ H ₅	1755-1670		(5) 7-7.63 (m)	(1) CH, 4.33 (q) (3) Me, 1.77 (d) J = 7 Hz
IIId	<i>p</i> -C ₆ H ₄ Me	1775-1650		(4) C ₆ H ₄ , 7-7.33 (m) (3) Me, 2.38 (s)	(1) CH, 4.32 (q) (3) Me, 1.76 (d) J = 7 Hz

Anal. Calcd. for C₁₀H₁₅NO₂S: C, 56.32; H, 7.09; N, 6.57; S, 15.00. Found: C, 56.30; H, 7.11; N, 6.60; S, 15.03.

Compounds II and III.

Compound I (2 g.) was refluxed for 5 hours in a solution of 20 ml. of 10% sulfuric acid in ethanol (50 ml.); the solution concentrated *in vacuo* yielded II and III.

Compounds III, IV, V and VI.

Phenyl and *p*-tolyl derivatives gave compounds III, IV, V and VI, which are known, together with I, II and VIII.

Compound Ic.

The spectral data for this compound are listed in Table II.

Anal. Calcd. for $C_{16}H_{14}N_2OS$: C, 68.07; H, 5.00; N, 9.92; S, 11.33. Found: C, 68.03; H, 5.04; N, 9.89; S, 11.35.

Compound Id.

The spectral data for this compound are listed in Table II.

Anal. Calcd. for $C_{18}H_{18}N_2OS$: C, 69.66; H, 5.85; N, 9.03; S, 10.31. Found: C, 69.64; H, 5.87; N, 9.00; S, 10.33.

Compound Iic.

The spectral data for this compound are listed in Table III.

Anal. Calcd. for $C_{10}H_9NO_2S$: C, 57.97; H, 4.38; N, 6.76; S, 15.44. Found: C, 57.91; H, 4.40; N, 6.73; S, 15.46.

Compound IId.

The spectral data for this compound are listed in Table III.

Anal. Calcd. for $C_{11}H_{11}NO_2S$: C, 59.72; H, 5.01; N, 6.33; S, 14.46. Found: C, 59.55; H, 5.28; N, 6.45; S, 14.32.

Compound VIIIc.

The structure of this compound will be investigated later.

Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.40; H, 6.18; N, 9.60.

Compound VIIIId.

The structure of this compound will be investigated later.

Anal. Calcd. for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.48; H, 6.92; N, 8.71.

Preparation and Characterization of Different Crystalline Structures of 3-*p*-Tolyl-5-methyl-2,4-thiazolidinedione (IId).

Compound IId shows a wide melting range (104-132°) after repeated recrystallizations from various solvents (ether, carbon tetrachloride, ethanol, etc.). Extended prismatic needles, melting at 118-120° (F II), were obtained by rapidly evaporating off the solvents used for recrystallization, followed by precipitation from an ethanolic solution of the mixture upon addition of water. The structure F II, upon grinding or by heating at a temperature above its melting point (~140°), followed by rapid cooling of the melt, gave agglomerate microcrystals (F I), having a lower-melting point (106-108°). The latter was also obtained by evaporating a solution of F II in acetone to dryness on a water bath. Structures F I or F II or the mixture was dissolved in a suitable volume of acetone forming a saturated solution at the boiling point of the solvent. The solution was allowed to stand and cool at 0° until most of the solid crystallized out; rectangular prisms separated off by filtration and were stored in a desiccator (F III). These crystals have a higher melting point (145-148°).

The three crystalline structures are unstable at room tem-

perature; they crystallize out from several solvents as a mixture, m.p. 104-132°. The ir spectra of F II and F III in nujol mull are identical [cm^{-1} : 1765-1693 (ν C=O), 2855 (ν C-H), 1380-1370 (δ C-H)], whereas F I has a somewhat different spectrum [cm^{-1} : 1755-1675 (ν C=O), 2875 (ν C-H), 1360 (δ C-H)] (Figure 1).

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